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I, LEANNE MYNOTT, MANAGER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2003906428 for a patent by INTERNATIONAL SCIENTIFIC PTY LTD as filed on 21 November 2003.

WITNESS my hand this
Third day of December 2004

LEANNE MYNOTT
MANAGER EXAMINATION SUPPORT
AND SALES

APPLICANT: International Scientific Pty Ltd
10 Koeppe Road
Claremont 6010
Western Australia

INVENTOR: Jeffrey D Edwards

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AUSTRALIA
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PROVISIONAL SPECIFICATION

FOR THE INVENTION ENTITLED:

"Electroporation enhanced transdermal delivery and stimulated bio-incorporation of therapeutic compounds in vivo"

Title of the Invention:

"Electroporation enhanced transdermal delivery and stimulated bio-incorporation of therapeutic compounds in vivo"

The invention is described in the following statement:-

The present invention can be described as an electromagnetic field generation device for the propagation of specifically configured EM fields of such characteristics to induce electroporation and biomimetic bio-effects in the target tissues of animals and humans in vivo, for the purpose of enhancing the transdermal delivery and bio-incorporation of ions, drugs, macromolecules, DNA fragments, genes, therapeutic and beneficial compounds

Background to the invention:

The present invention relates to the trans-dermal delivery of beneficial compounds and more particularly to the use of induced electroporation as a means of enhancing the application and utility of trans-dermal delivery in vivo. Additionally the present invention also relates to the use of induced bio-mimicry as a means of encouraging or stimulating bio-uptake and utilisation of said therapeutic compounds that have benefited from the enhanced transdermal delivery in an in vivo environment.

The use of therapeutic compound in the treatment and avoidance of disease, injury or disability has been a corner-stone of medical care in both humans and animals for many centuries.

For such therapeutic agents to be useful, they must be physically and/or chemically available to the local biological system and also available in such form and/or concentrations so they may exerts some beneficial biological effect over the biological process, disease, injury or disability.

Transdermal delivery provides a convenient delivery pathway for some therapeutic substances as they may be applied with some degree of site specificity and in a form

unaltered by digestion and blood chemistry. Additionally, transdermal delivery offers the possibility of high user compliance, easy of dose management, low toxicity and high cost effectiveness.

Unfortunately, mammalian skin poses a significant barrier to the entry for many therapeutic agents, as the lipid bilayer that makes up the cell membrane, usually presents hydrophobic temporary aqueous pore that will only allow the passage of small (~1nm size) neutrally changed particles. For these reasons, transdermal delivery of many ions, drugs, macromolecules, DNA fragments, genes and therapeutic compounds is less effective and efficient than other delivery methods such as injection. In an attempt to overcome this, a number of electro-kinetic approaches have been developed.

Iontophoresis for example, uses electrical energy gradients to charge a target molecule, then ram it through the cell membrane using electro-motive force. This technique can be unsuitable for general application due to residual cellular damage, changes to critical ionic structures within the therapeutic compound being delivered and localised burns, skin irritation and cellular fatigue.

Contact electroporation is another electrokinetic process but more suited to in vitro applications. Contact electroporation is unsuited to in vivo usage as physical and electrical contact with the target cellular environment and the therapeutic agent is required. Additionally, the contact electroporation pulse characteristics of a 1 to 10 ms pulse of 100 to 200 volts poses significant and as yet unexplored dangers for living organisms.

In addition to the difficulties and complexities that relate to the delivery of ions, drugs, macromolecules, DNA fragments, genes, therapeutic and beneficial compounds to the local biological system in adequate therapeutic concentrations, the desired beneficial influence cannot necessarily be assumed simply by local presence alone.

Many biological systems and processes require stimulation or specific events to occur, prior to such therapeutic ions, drugs, macromolecules, DNA fragments, genes, therapeutic and beneficial compounds being taken up and utilised by the target systems.

Such a situation can be illustrated in the case of common un-uniting or delayed union following an osseous fracture. Making osteoblastic nutrients or bone precursors available at the site of injury, either trans-dermally., through nutritional supplements, orally or by injection, will not guarantee union. Physical exercise or more accurately, specifically configured bioelectrical events are believed to be an essential osteoblastic stimuli and without such stimuli, union is unlikely to occur, irrespective of the levels of available therapeutic compounds.

Conversely, the stimuli necessary to instigate biosynthesis, repair and other beneficial biological processes alone may be ineffective at achieving the desired outcomes if such stimuli is associated with a low levels of available bio-nutrients.

It would therefore be desirable to provide a method and apparatus for the electroporation enhanced transdermal delivery of therapeutic compounds suitable and safe for use in an in vivo application.

It would additionally be desirable to provide electroporation enhanced transdermal delivery of therapeutic compounds in such a manner that the electroporative effect could be induced non-invasively through the accumulation of repeated EMF bio-effect, rather than propagated by means of electrical contract.

It would also be desirable to provide induced electroporation enhanced transdermal delivery of therapeutic compounds in association with induced bio-mimetic stimuli of the type and character known to stimulate the incorporation of therapeutic compounds.

With these objectives clearly in mind, the present invention provided:

An electromagnetic coil, energy supply and controller means for the production and propagation of a low frequency time varying magnetic field for the purpose of inducing specific ionic currents in tissues such as, but not limited to, the lipid bilayer of cells found in the epidermis, dermis and subcutaneous layers.

The present invention can be considered as having 2 essential components.

These are:

- a means of producing and propagating a low frequency time varying electro-magnetic field (EMF) of repetitive frequency or frequency pattern of between 1 and 100 Hz with a pulse duration between 1us and 1 second.
- a means for exposing the target tissues to such EMF for the purpose of inducing electroporation and or biomimetic effect.

The present invention can be considered to have 2 essential functional components.

These are:

- an EMF for the purpose of inducing temporary aqueous pores by the process known as electroporation
- An EMF for inducing bio-mimetic stimuli substantial similar to those known to assist in bio-incorporation and bio-uptake in various target tissues.

The present invention will be better understood with reference to the follow description:

The present invention can be considered as an electromagnetic field generation device for the propagation of specifically configured EM fields of such characteristics to induce electroporation and biomimetic bio-effects in the target tissues of animals and humans for the purpose of enhancing the efficiency of transdermal delivery and the bio-incorporation of ions, drugs, macromolecules, DNA fragments, genes, therapeutic and beneficial compounds.

In one possible embodiment, the present invention may be deployed as a programmable controller device that supplies specifically configured electrical current to a coil inductor, either integrated with or connected to the said programmable controller device.

The desirable ions, drugs, macromolecules, DNA fragments, genes, therapeutic and beneficial compounds that are to be delivery transdermally may be applied topically to the skin prior to exposure to the beneficial EM fields, or equally, may be applied to the surface of the inductive unit for secondary transfer to the skin during exposure.

The EM field may be, but not necessarily, specifically programmed and configured to induce the energy and impulse required to achieve the desired pore size, number, density and membrane breakdown required to achieve efficient electroporation of a particular ion, drugs, macromolecules, DNA fragments, genes, therapeutic or beneficial compound.

The EM field may be, but not necessarily, followed by a different EM field designed to induce iontopheretic forces within the membrane structure to enhance the migration of ions, drugs, macromolecules, DNA fragments, genes, therapeutic and beneficial compounds through the induced temporary pores.

The EM field may yet again, but not necessarily, be followed by a different EM field designed to close the induced pores and restore membrane integrity.

The EM field may subsequently, but not necessarily, be followed by a different EM field designed to induce a biomimetic phenomena in the target tissues for the purpose of stimulating bio-uptake and bio-incorporation of the introduced ions, drugs, macromolecules, DNA fragments, genes, therapeutic and beneficial compounds.

By inducing such bi-mimetic stimuli in association with the efficient introduction of ions, drugs, macromolecules, DNA fragments, genes, therapeutic and beneficial compounds through induced electroporation enhanced transdermal delivery, the present invention achieves the objectives of providing electroporation enhanced transdermal delivery and stimulated bio-incorporation of therapeutic compounds for use in vivo in both humans and animals.

Numerous variations and embodiments will suggest themselves to a person skilled in the relevant technical arts, in addition to those already disclosed , without departing from the basic inventive concept.

For example, the present invention will find utility in cases involving ions, drugs, macromolecules, DNA fragments, genes, therapeutic and beneficial compounds that may be initially introduced to the body orally or by injection, rather than transdermally. Such variation should be considered within the scope of the present invention if the trans-membrane migration of the introduced ions, drugs, macromolecules, DNA fragments, genes, therapeutic and beneficial compounds is assisted by inductive electroporation and augmented by inductive biomimetic phenomena, as disclosed in the present invention.

It will be apparent to a person skilled in the art that the disclosed invention has been described in some detail for the purpose of clarity and understanding, and that various modifications and alterations to the embodiments and methods, as set out in the example above, are both possibly and beneficial to the utility of the present invention.

All such additions and variations are possible without deviating from the innovation and benefits of the invention. Such deviations and variations fall within the inventive concept disclosed in this specification.

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Jeffrey D Edwards

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